GIVEN TO RECIPIENT

STAYS IN DONOR

Interior Verna Cava

Split

Bile

Hepatic Artery

Portal Vein

Right Hepatic Vein

Oversewn Right Hepatic Vein

Hepatic Vein

Right Hepatic Artery

Left Hepatic Vein

Right Portal Vein

Right Bile Duct Stump

Right Bile Duct

Bile Duct

Portal Vein

Hepatic Artery

Recipient's Liver

Lungs
Heart
Stomach
Spleen
Colon

Donor's Liver

Lungs
Heart
Stomach
Spleen
Colon

Regeneration
in 6-8 weeks

Liver transplantation to replace the damaged organ in an adult patient with liver disease can now be performed using a partial liver from a living donor. In this procedure, the right lobe of the donor's liver (in blue) is removed and transplanted into the recipient. In both donor and recipient, regeneration of the partial liver takes place, such that full size is attained in 6-8 weeks. While this procedure has the potential to alleviate the current crisis in availability of organs for transplant, it currently carries some risks for both donor and recipient. In children with end-stage liver disease, a left-lobe living donor operation can be performed, which carries less risk for the donor. Adapted and used with permission from the Liver Transplant Programs, Keck USC School of Medicine and Childrens Hospital Los Angeles.

CHAPTER 12:
LIVER TRANSPLANTATION

INTRODUCTION AND BACKGROUND

Liver transplantation is now considered the standard of care for patients with end-stage liver disease or acute liver failure. Orthotopic liver transplantation involves removal of the diseased organ and replacement with a liver from a deceased donor. In some situations, particularly in pediatric liver transplantation, a portion of the donor liver is used (reduced size liver graft) or a single liver is shared between two recipients (split liver grafts). In other cases, a partial liver graft from a living donor is used to replace the damaged organ (living donor liver transplantation). In children, the left lobe (or left lateral segment) of a liver from a living adult can be used in living donor liver transplantation. In adults, a right lobe of a liver from a living donor must be used to provide an adequate liver mass. More than 5,000 liver transplants are performed in the United States each year at approximately 120 medical centers that specialize in this procedure. Approximately 500 of these transplants are done in children, of which at least a third are from living donors. In adults, living donor liver transplantation currently accounts for only 5 percent of transplants.

The major indication for liver transplantation is chronic end-stage liver disease. Other indications include liver cancer, acute liver failure, and life-threatening metabolic liver disease, such as Crigler-Najjar syndrome. Currently, the major reason for liver transplantation in adults is chronic hepatitis C, and other important reasons include alcoholic liver disease, primary biliary cirrhosis, sclerosing cholangitis,

autoimmune hepatitis, hepatitis B, nonalcoholic steatohepatitis, and cryptogenic cirrhosis. Hepatocellular carcinoma has become an increasingly common reason for transplantation, usually in patients who have an underlying compensated cirrhosis. Acute liver failure accounts for 8 percent of transplants in adults and 12 percent in children. In children, the major reasons for liver transplantation are biliary atresia, neonatal cholestatic liver diseases, and acute liver failure.

The success of liver transplantation has improved markedly in the last two decades. At present, one-year patient survival after transplantation averages 85 percent and 5-year survival is approximately 70 percent. Survival rates vary to some extent by the indication for transplantation, with the best 5-year survival among patients undergoing transplantation for primary biliary cirrhosis and sclerosing cholangitis. Outcomes are less successful in patients with chronic hepatitis C, alcoholic cirrhosis, and hepatocellular carcinoma.

The increasing success rate of transplantation has led to an increase in demand, particularly in the past ten years. Currently, over 17,000 patients are awaiting a liver transplant in the United States. In contrast, the number of liver donors has increased only modestly, to approximately 5,000 donors annually, and nearly 2,000 candidates die while awaiting liver transplantation each year. The increasing gap between supply and demand has affected practice patterns, with growing use of the surgical variants noted

above, and with added stress on the organ allocation system. In 2002, the Model for End-stage Liver Disease (MELD) system was introduced, which uses laboratory results for bilirubin, prothrombin time, and creatinine to calculate a score that indicates the likelihood of survival if liver transplantation is not performed. Use of the MELD score places primary emphasis on severity and likelihood of survival rather than time of referral or diagnosis. After 1 year of using the MELD system, the waiting list mortality has decreased. A similar system has been developed for pediatric liver transplantation (Pediatric model for End-stage Liver Disease, or PELD), which calculates a score based on age, growth failure, and laboratory values for bilirubin, albumin, and prothrombin time.

RECENT RESEARCH ADVANCES

Several advances have been made since human liver transplantation was first developed in the 1960s.

Immunosuppression: Initially, the success of liver transplantation was limited by technical challenges, problems with graft rejection, the need for high doses of immunosuppression, and the frequency of infectious complications. With the introduction of more effective regimens to prevent rejection in the early 1980s, liver transplantation transitioned from an experimental procedure with poor long-term survival to the standard therapy of patients with acute or chronic liver failure. Improved immunosuppressive regimens have also allowed for better quality of life for transplant recipients and alleviated problems with acute and chronic rejection. The decrease in frequency of chronic rejection in the past decade is testimony to this progress. At the same time, it has become clear that the requirement for immunosuppression after liver transplantation represents a dynamic process that declines as a successful liver transplant matures. In the late 1980s, introduction of a more

effective preservation solution allowed for longer delay between donor organ retrieval and placement of the liver graft, which made liver transplantation a semi-elective procedure, allowed for transport of livers over long distances, and improved early graft function and survival rates.

Improved Techniques and Management: Patients undergoing liver transplantation have also benefited from improved surgical and anesthetic techniques and better means of management of the complications of liver transplantation. The current excellent outcomes of liver transplantation attest to the enormous progress made in basic and clinical research on organ transplantation.

Living Donor Liver Transplantation: Despite the many advances, the last 10 to 15 years have also seen major emerging challenges in liver transplantation. The single, most critical problem has been the crisis in donor liver availability. Since 1992, the size of the waiting list for liver transplantation has exceeded the number of transplants performed each year. With each passing year, this discrepancy between supply and demand of organs has widened. The response to the donor crisis has led to a broad array of approaches to correct this shortage.

Most practical, but also most controversial, has been living donor liver transplantation. Use of partial grafts from living donors was first introduced into pediatric transplantation in 1989 and has become a standard procedure, accounting for a third of transplants in children. The procedure usually involves donation of the left lateral segment of the liver from a parent or relative of a child. The success rate of pediatric, living donor liver transplantation is similar to deceased donor liver transplantation, and donor acceptance and survival without long-standing morbidity has been excellent. Use of living donors was introduced into adult liver transplantation in the mid-1990s in Japan and in 1998 in the United States.

The ethical and medical issues raised by this procedure are many. The major challenge of the operation in adults is that survival of the recipient requires use of the right lobe of the liver, which usually constitutes 60 percent of the liver mass. For this reason, the donor operation in adult-to-adult living donor liver transplantation is a potentially life-threatening operation. Indeed, the mortality rate for the donor is in the range of 1 in 250 to 1 in 500, a risk that is challenging and must be seriously weighed in the decision to perform the operation. Nevertheless, adult-to-adult living donor liver transplantation is now done by at least 50 transplant centers in the United States and accounts for 5 to 10 percent of adult transplants.

Other Challenges in Liver Transplantation: In the early 1990s, tests for hepatitis C first became available and soon revealed that at least a third of liver transplants done in adults each year were performed for end-stage chronic hepatitis C. Unfortunately, testing showed that hepatitis C invariably recurred in the transplanted liver, leading to a risk of progressive disease graft loss over time. Current therapy has been disappointing for post-transplant hepatitis C, making the development and assessment of better approaches a priority.

Another major challenge in liver transplantation is the increasing incidence of hepatocellular carcinoma in the United States. The prognosis of liver cancer is poor, and the presence of underlying cirrhosis in most patients makes therapy more difficult. Chemotherapy is largely ineffective and local treatments are only palliative. Surgical resection may be possible for small tumors, but the presence of cirrhosis makes the operation dangerous, and the recurrence rate even after successful surgery is very high. In contrast, liver transplantation for hepatocellular carcinoma can lead to long-term survival without recurrence and with resolution of the underlying liver disease. One difficulty is that the criteria for transplantation

for hepatocellular carcinoma restrict its use to only a small proportion of patients with this tumor.

Thus, research advances have significantly improved the success rate of liver transplantation procedure, but many challenges to its use remain.

RESEARCH GOALS

The ultimate goals of research in liver transplantation are to optimize the availability and long-term success of liver transplantation as a treatment of acute and chronic liver failure and to provide means to reliably diagnose, manage, treat, or prevent its major complications.

Basic Research: The success of liver transplantation is dependent upon prevention of allograft rejection and maintenance or induction of long-term graft tolerance. Acute cellular rejection is common after liver transplantation, but, with current advanced regimens of immunosuppression, most instances of rejection are self-limited. Chronic ductopenic allograft rejection is uncommon. The decrease in rejection, however, comes with a price of complications of immune suppression. Indeed, the major causes of morbidity and mortality after liver transplantation, aside from those associated with the surgery itself, are largely the complications of immunosuppressive therapy, such as bacterial, viral, and fungal infections; hypertension; diabetes; hypercholesterolemia; weight gain; renal disease; depression; neuropathy; bone disease; and increased risk of cancer.

The metabolic abnormalities associated with immunosuppressive therapies also predispose liver recipients to the long-term consequences of coronary and cerebrovascular artery disease. The long-term development of renal failure is a major source of morbidity and mortality in recipients of extrarenal organs. These

complications are all the more important for children and young persons undergoing liver transplantation who will live with the transplant for many decades. While better immunosuppressive agents may help in solving many of these problems, the ultimate goal is to induce and maintain recipient immune tolerance, such that immunosuppressive drugs can be stopped with maintenance of good liver transplant function.

- *Research Goal:* To better understand the immunologic interplay between the host and the liver graft, which, in some cases, leads to acquired tolerance (Matrix Cell B2).
- *Research Goal:* To translate such knowledge into more effective, tolerance-inducing therapy (Matrix Cell C2; see also Chapter 10, Matrix Cell B1).

State-of-the-art methodologies to investigate the molecular pathways and cytokine networks involved in graft recognition and the development of tolerance could be applied in both animal models and patients to help define pathways that lead to recurrent problems with rejection vs. tolerance.

With the advent of living donor liver transplantation and use of partial grafts, optimizing liver regeneration has become an important issue in liver transplantation. Regeneration of the residual donor liver and growth of the partial donor graft in the recipient are both necessary for the safety and success of this procedure. Delineation of the necessary cell signaling pathways, gene regulatory elements, and cytokine networks that induce and regulate regeneration would help to improve the efficacy and safety of living donor liver transplantation.

- *Research Goals:* To better delineate the cellular mechanisms of liver regeneration and identify targets for drugs or cytokines to promote or maintain regeneration during the critical periods of living donor liver transplantation (Matrix Cells A3 and B3; see also Chapter 3, C2).

Clinical Investigation: At present, the diagnosis of acute rejection is based upon the pattern and timing of liver enzyme abnormalities after transplantation, which is generally supplemented by findings from liver biopsy. The degree of abnormalities in enzymes, however, is not a very accurate means of assessing the severity of the rejection episode, and the findings are confounded by the many potential causes of liver enzyme abnormalities in the peritransplant period. For example, differentiating recurrent hepatitis C from acute rejection can be very difficult, even with liver biopsy.

Standard histologic examination of the liver may not fully distinguish between alloimmune-driven cellular infiltrates, graft injury, and damage initiated by other pathways, or the combination of insults. Biomarkers detected in serum for rejection and its severity would be of great benefit in management of patients.

- *Research Goal:* To develop biomarkers for acute cellular rejection and its severity (Matrix Cell A2).

The use of gene array studies on patient lymphocytes and liver tissue and proteomic analyses on plasma are appropriate and possibly valuable means of developing biomarkers for the diagnosis and staging of rejection.

Just as important, if not more so, is the development of a more accurate means of assessing the adequacy of immunosuppression. At present, the dosage of immunosuppression is usually guided by serum levels of the agent and signs of clinically apparent rejection. Sensitive and accurate biomarkers for rejection and tolerance would be helpful in individualizing therapy and avoiding both over- and under-immunosuppression. In particular, precise quantitation of the total magnitude of immunosuppression achieved with different regimens is desirable.

• *Research Goal:* To identify biomarkers for acute cellular rejection or that reflect the adequacy of immunosuppression (Matrix Cell A2).

Therapy and Clinical Trials: There have been many industry-supported trials of immunosuppressive agents in liver transplantation, and several potent immunosuppressive agents are now available. Most of these studies were short-term trials, and endpoints of success were prevention of acute cellular rejection during the first 3 to 6 months after transplantation. An important goal now is the initiation of more ambitious studies aimed at developing tolerance-inducing regimens with endpoints of patient and graft survival and long-term improvement in quality of life. Such studies would be particularly helpful in children, who are often not included in pivotal studies of new immunosuppressive agents.

• *Research Goal:* To define factors associated with successful pediatric liver transplantation in terms of growth and development, school performance, and social and intellectual development through a careful prospective and long-term assessment (Matrix Cell C1; see also Chapter 10, B1).

Post-transplant lymphoproliferative disease (PTLD) is a severe and potentially fatal malignancy that occurs after transplantation, apparently due to *de novo* infection with Epstein Barr Virus. PTLD is particularly a problem after pediatric liver transplant.

• *Research Goal:* To develop practical and effective means of preventing PTLD (Matrix Cell B3).

Another important issue in long-term survivors after liver transplantation is detection of natural allograft tolerance. A small proportion of patients with a liver transplant can be completely withdrawn from immunosuppressive therapy. Unfortunately, the ability to stop all immunosuppression is uncommon, and most patients will develop severe and potentially

life-threatening rejection if immunosuppressive therapy is stopped.

• *Research Goal:* To identify factors that predict and biomarkers that reflect tolerance and the ability to stop immunosuppressive therapy through careful prospective studies of immunosuppression withdrawal regimens supported by intense immunologic monitoring (Matrix Cell C2).

Use of state-of-the-art methods, such as gene arrays and proteomics, may well provide insights into factors that underlie tolerance in this situation and demonstrate what serum or hepatic proteins or genes are important in acquired tolerance. Such studies could focus on molecular mechanisms of tolerance with careful assessment of MHC matching, minor histocompatibility issues, chimerism, and the role of the innate immune system.

In adults, hepatitis C is currently the single most common reason for liver transplantation, and its management post-transplantation still poses several challenges.

• *Research Goal:* To develop a means of preventing recurrence of hepatitis C after transplantation (Matrix Cell C3; see also Chapter 5, C2).

Appropriate approaches might include use of peginterferon and ribavirin before, during, or after transplantation; use of hepatitis C immune globulin; or use of newer antiviral agents, adoptive immunotherapy, or gene therapy to attempt to eradicate virus.

• *Research Goal:* To develop better means to treat hepatitis C recurrence post-transplant (Matrix Cell B1; see also Chapter 5, A1).

Peginterferon and ribavirin have limited efficacy in this situation and are often poorly tolerated.

- *Research Goal:* To develop improved antiviral agents and regimens with better tolerability to help this important population of patients with hepatitis C (Matrix Cell B2; see also Chapter 5, C1).

However, not all patients who have recurrence of HCV infection develop significant hepatitis. Factors that determine the severity of recurrent disease and pathways that maintain virus replication without major cellular injury also require investigation. The application of newer research technology to these issues is acutely important.

Hepatocellular carcinoma has become a major indication for liver transplantation in recent years, and the rising incidence of liver cancer threatens to exacerbate the current shortage of liver organs for transplantation.

- *Research Goal:* To develop therapeutic approaches to the management of liver cancer before, during, and after liver transplantation (Matrix Cell C1; see also: Chapter 14, B1; Chapter 16, A1).

Thus, clinical trials are warranted to better assess the efficacy of pre-transplant chemoembolization or local ablative therapies in preparation for liver transplantation. Furthermore, the role of adjuvant and post-transplant chemotherapy is important to assess in a prospective manner.

An urgent issue in liver transplantation is finding ways to increase the availability of organs. The current organ shortage has resulted from an increasing demand for liver transplantation, which has not been met with a commensurate increase in donor organs. There are several ways in which research might help alleviate the organ shortage. First, with improvements in living donor liver transplantation, this challenging and controversial approach might be made safer and more effective.

- *Research Goal:* To improve the safety and efficacy of living donor liver transplantation (Matrix Cell B1).

A second approach to improving availability of livers for transplantation is optimizing the allocation of organs based upon both need and outcome. The introduction of the MELD and PELD systems for assessing the need for liver transplantation appears to have led to an important decrease in waiting list mortality. However, these systems can certainly be refined and means can be developed to individualize the scoring method based upon carefully collected information on outcomes from national and multicenter registries.

- *Research Goal:* To further refine the MELD and PELD systems in order to optimize the allocation of livers for transplantation (Matrix Cell A1).

A third option to explore in order to increase the availability of livers for transplant is to develop better ways of assessing so-called "extended criteria" donors (e.g., non-heart-beating donors) and improving the function of grafts from donors that are considered high risk because of size, fatty infiltration, prolonged ischemia time, or advanced age. Enhancing the function of these livers and better matching of donors with appropriate recipients would improve organ availability and outcome.

Innovative approaches to increasing the availability of livers for transplant include use of xenografts (organs from other species, such as pigs), hepatocyte transplantation, and stem cell therapy. At present, these approaches are impractical, but continued, focused research in these areas is warranted. Hepatocyte transplantation and gene therapy are particularly suitable as means for replacing liver transplantation for inherited metabolic liver diseases such as Crigler-Najjar syndrome, in which the liver is normal except for a single gene defect.

- *Research Goal:* To develop gene or cell therapy for at least one metabolic liver disease that delays or replaces liver transplantation (Matrix Cell C3; see also Chapter 3, C1).

Finally, research on organ donation, including finding means to increase public acceptance of donation, would be beneficial to pursue. At present, only half of the organs that could be used in liver transplantation are donated. The social, ethical, and psychological issues that lead families to refuse organ donation require careful study.

Living donor liver transplantation represents a critical area in research on liver transplantation. The recently formulated Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) provides a mechanism for a network of prospective studies on this procedure and could be used to pursue all of the goals apropos of liver transplantation. Similarly, the currently funded Studies of Pediatric Liver Transplantation (SPLIT) is a very appropriate means to advance clinical research and clinical trials in pediatric transplantation.

STEPS TO ACHIEVE RESEARCH GOALS

Basic research on immune tolerance and allograft rejection is important to continue as an area of high program relevance. Induction of tolerance is important for all forms of organ transplantation, including liver transplantation. Studies can be funded through the "Immune Tolerance Network," which maintains a databank and funds many studies on immune tolerance and tolerance-inducing regimens of therapy.

The Scientific Registry of Transplant Recipients (SRTR) collects important demographic, clinical, laboratory, radiological, histologic, and outcomes data on all patients undergoing liver transplantation in the United States. This database is a powerful tool for epidemiological and clinical investigation and should be fully used to provide reliable information on liver transplantation. This system is particularly suited for ongoing assessment of the MELD and PELD criteria and other approaches to improve the allocation system.

Matrix of Research Goals in Liver Transplantation

	Short Term (0-3 years)	Intermediate Term (4-6 years)	Long Term (7-10 years)
High Risk	**A3.** Elucidate pathways of liver regeneration and identify targets for drug or cytokine/anticytokine therapy.	**B3.** Elucidate the pathogenesis of PTLD and means of prediction, prevention, and control. Develop means of improving regeneration after living donor liver transplantation.	**C3.** Develop means to prevent recurrence of hepatitis C after liver transplantation. Develop gene or cell therapy for at least one metabolic liver disease that delays or replaces liver transplantation.
Intermediate Risk	**A2.** Identify biomarkers for acute cellular rejection and adequacy of immune suppression.	**B2.** Delineate molecular pathways of immune tolerance to allografts in humans. Develop new therapies for hepatitis C that are effective in the transplant situation.	**C2.** Based upon molecular mechanisms, develop and assess tolerance-inducing regimens, including studies in children. Identify biomarkers that predict tolerance and the ability to discontinue immunosuppression after liver transplantation.
Low Risk	**A1.** Develop further refinements in the MELD and PELD systems that optimize allocation of livers for transplantation.	**B1.** Define efficacy of peginterferon and ribavirin in pre- and post-transplant HCV infection. Improve safety and define role of living donor liver transplantation.	**C1.** Define factors important in long-term success of liver transplantation in children as defined by quality of life and social and psychological development. Determine efficacy of chemotherapy and local ablative treatment of HCC done in the peri-transplant period.